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Polycystic Ovaries Associated with Congenital Adrenal Hyperplasia

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ABSTRACT

Polycystic ovaries were found in a 16-year-old female with congenital absence of vagina, male-like external genitalia, and congenital adrenal hyperplasia. Masculinization was sufficiently severe to cause the patient to be reared as a male. Biochemical studies of ovarian tissue revealed hyperactivity and an imbalance of enzyme systems concerned with steroid-hormone biosynthesis, which led to production of large amounts of androgens. The pathway towards estrogens was preserved but less efficient than normal. Urinary steroid metabolites before and after hysterectomy and bilateral salpingo-oophorectomy revealed an absence of Porter-Silber chromogens and tetrahydrocortisone. Excretion of aldosterone was normal and that of corticosterone slightly higher than normal. The patterns of urinary 17-ketosteroids, pregnanediol, pregnanetriol and pregnanetriolone were similar to those commonly seen in congenital adrenal hyperplasia with steroid 21-hydroxylase deficiency. Urinary estrogens after panhysterectomy were low, being in the post-menopausal range. The pathogenesis of polycystic ovaries and their possible contribution to masculinization are discussed.

SOMMAIRE

On a découvert des ovaires polykystiques chez une fille de 16 ans qui présentait une absence de vagin, d'origine congénitale, des organes génitaux externes semblables à ceux du mâle et une hyperplasie surrénale congénitale. La masculinisation était assez prononcée pour qu'on l'élève comme un homme. L'étude biochimique des ovaires a révélé une hyperactivité et un déséquilibre des systèmes enzymatiques, relative à la biosynthèse de l'hormone surrénale qui aboutissait à la sécrétion de fortes quantités d'androgènes. Le processus d'élaboration des estrogènes était conservé, mais moins actif que la normale. L'analyse des métabolites urinaires des stéroïdes, faite avant et après hystérectomie et salpingo-ovariectomie bilatérale a montré l'absence des chromogènes de Porter-Silber et de tétrahydrocortisone. L'excrétion d'aldostérone était normale et celle de corticostérone légèrement supérieure à la normale. Les courbes d'excrétion urinaire de 17-cétostéroïdes, du prégnandiol, de prégnantriol et de prégnantriolone étaient voisines de celles qu'on observe couramment dans l'hyperplasie surrénale congénitale, avec une insuffisance de 21-hydroxylase corticoïde. Les estrogènes urinaires après hystérectomie totale étaient pauvres et se situaient dans la gamme de ceux qu'on trouve après la ménopause. La pathogénie des ovaires polykystiques et leur contribution à la genèse de la masculinisation sont étudiées par les auteurs.

OVARIES morphologically similar to those seen in Stein-Leventhal syndrome have been observed in several cases of virilizing congenital adrenal hyperplasia.[1, 2] We recently had an opportunity to study the biosynthesis of steroid hormones by polycystic ovarian tissue obtained from a female pseudohermaphrodite, and urinary steroid excretion before and after panhysterectomy.

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CASE REPORT

A 16-year-old patient of very short stature and with hypospadias was admitted for investigation. At birth this patient was accepted as male and he was raised as such. He always enjoyed good health, and during childhood attempts were made to repair the hypospadias. Linear growth ceased between the ages

Canad. Med. Ass. J.
Jan. 1, 1966, vol. 94

of 12 and 14 years, and at this time male secondary characteristics (change in voice and appearance of facial, pubic and axillary hair) developed. Beginning at age 15 the patient shaved once or twice a week. The family history did not reveal any congenital abnormalities. His parents are of short stature (father 5′ 4″ and mother 5′ 3″) and both are in good health. His two sisters are normally developed.

On admission, physical examination revealed a well-nourished, short individual (4′ 11″) with short extremities, a male habitus, and a male type of hair distribution (Fig. 1). The body weight was 90 lb. and height considerably exceeded span (59″/51″). His head was relatively large, with a prominent lower jaw. In the pubic region there was a phallus-like structure with urethral opening below it, and some ill-defined skin folds resembling an empty scrotum. His blood pressure and pulse were normal and remained so throughout his hospitalization. The remainder of the physical examination was non-contributory. Radiological examination of the skull revealed frontal hyperostosis; the sella turcica was normal. Skeletal survey showed that the epiphyses of the hands, feet, knees, hips and iliac crests were fused and the pelvis was of female shape. Other radiological findings were normal.

The genetic sex determinations were done on buccal smears and the chromatin pattern was of female type. In spite of the genetic sex of a female, the patient will be referred to as "he", in order to conform with the environmental sex.

Blood serum biochemical analyses (sodium, potassium chloride, bicarbonate, calcium, phosphorus, alkaline phosphatase, fasting blood sugar, blood urea nitrogen) were within the normal limits.

Serum protein-bound iodine was 7.0 μg. % (normal: 4.0 to 9.0 μg. %). Urinary follicle-stimulating hormone (FSH) was not detectable. Gross abnormalities were observed in the excretion of urinary steroids with a high output of pregnanetriol, pregnanediol, pregnanetriolone and 17-ketosteroids, as commonly seen in congenital adrenal hyperplasia.[3-5] The Porter-Silber chromogens could not be detected. Detailed urinary steroid levels are given in the section on results.

Exploratory laparotomy in this patient disclosed enlarged, pale polycystic ovaries, normal Fallopian tubes, a small but anatomically normal uterus, absence of vagina, and bilaterally enlarged adrenal glands. Since the patient had been raised as a male, hysterectomy and bilateral-salpingo-oophorectomy was decided on. After operation, he was maintained on monthly injections of long-acting testosterone and daily doses of 37.5 mg. of cortisone. The patient at present is free from post-oophorectomy or "menopausal" symptoms and has undergone, without incident, a plastic revision of the external genitalia.

The surgical specimen of the internal female organs removed by panhysterectomy is shown in Fig. 2. Histological sections of the ovaries exhibited a striking similarity to polycystic ovaries commonly seen in patients with Stein-Leventhal syndrome (Fig. 3). The sections of the ovary presented evidence of hyperthecosis and multiple follicular cysts which were variable in size, suggesting follicular maturation arrest. Microscopic structure of the uterus revealed normal myometrium and a simple endometrium as commonly seen in prepubertal girls.

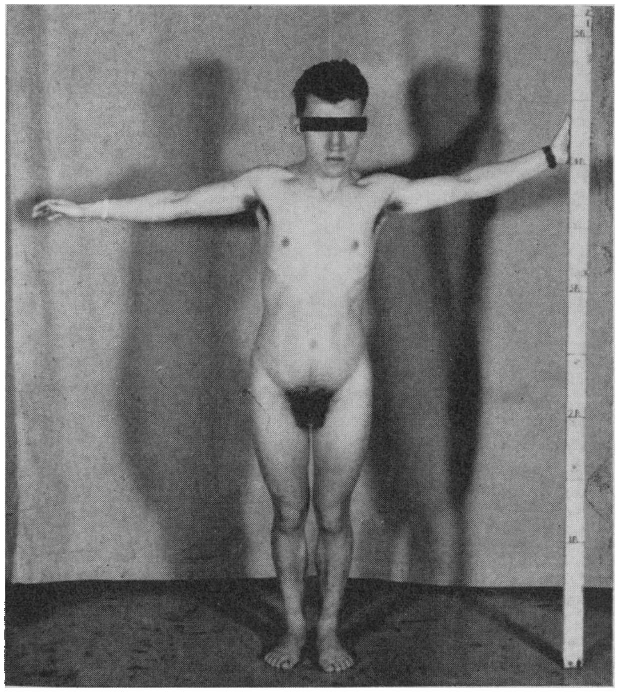

Fig. 1.—Patient at time of admission to hospital.

MATERIALS AND METHODS

(a) *Steroid metabolite assays in urine.*—The total urinary 17-ketosteroids were measured colorimetrically in terms of dehydroepiandrosterone

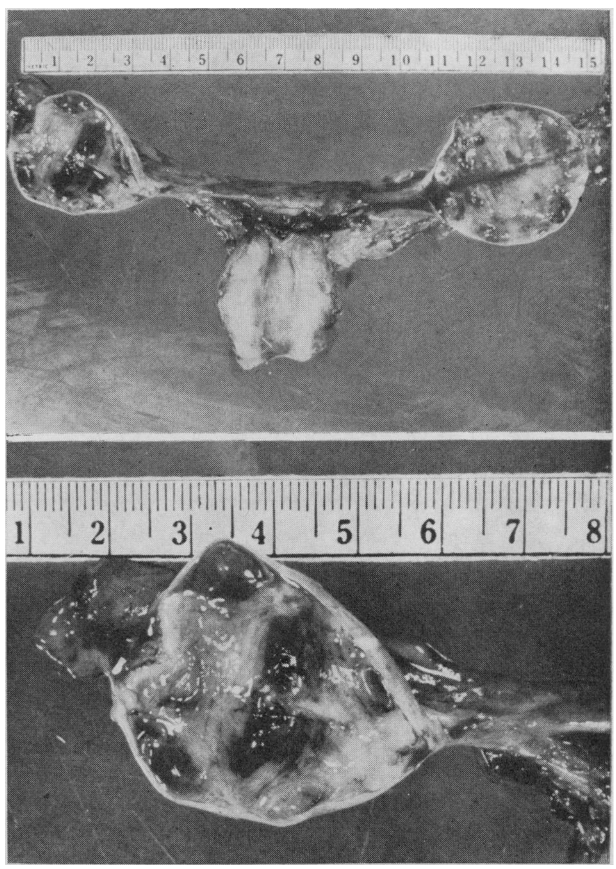

Fig. 2.—Surgical specimen of uterus, Fallopian tubes and ovaries.

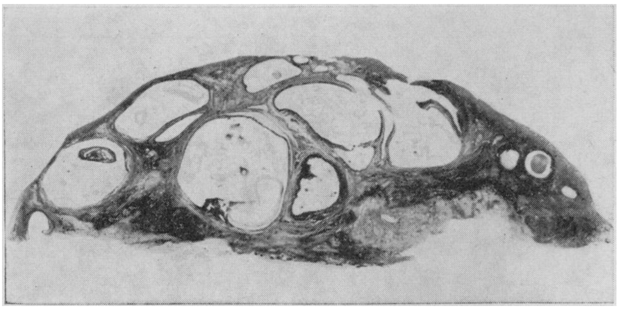

Fig. 3.—Histological section of the ovary.

standard.[6] For the assay of individual C19 steroids the urine was enzymatically hydrolyzed and "solvolyzed"[7] and the extracts were separated by means of thin-layer and paper chromatography. Final separation and measurement of neutral C19 steroid trimethylsilyl ethers was done in an F & M gas chromatograph. The assays of pregnanediol, pregnanetriol, Porter-Silber chromogens and THE (tetrahydrocortisone) were kindly carried out in Dr. E. H. Venning's laboratory, The Royal Victoria Hospital, Montreal. Pregnanetriolone was detected in the urine by the method of Finkelstein.[8] Urinary estrogens were fractionated by the method of Brown, Bulbrook and Greenwood[9] and the separated estrogen 3-methyl ethers were assayed fluorometrically, using the Ittrich[10] modification of the Kober reaction. Urinary conjugated and non-metabolized aldosterone and corticosterone were measured by double-isotope derivative techniques in the N.E. Biomedical Assay Laboratories, Boston, Mass.

(b) *Incubation of the ovarian tissue.*—The ovarian tissue after surgery was preserved in Krebs-Ringer solution cooled over ice. For incubation, a fine mince of the ovarian stroma was used. Weighed ovarian tissue preparations were incubated in glass vessels at 37.5° C. for three hours under 95% O_2 and 5% CO_2 in 20 ml. Krebs-Ringer bicarbonate buffer (pH 7.4) containing 200 mg. % glucose and the labelled steroid precursor. Incubation studies were performed, using as precursors progesterone-4-C^{14} (sp. act. 64.9 μc./mg.), testosterone-4-C^{14} (sp. act. 75.2 μc./mg.) and estrone-16-C^{14} (sp. act. 45.4 μc./mg.). In order to study the endogenous activity of the ovarian tissue no co-factors or stimulating substances were added to the incubation media.

After incubation the buffer and the tissue were extracted with rigid precautions to avoid cross-contamination with other samples. Labelled steroid hormones present in the extract were separated by means of paper, thin-layer and column chromatography. The radioactivity in crude extracts and in chromatographically separated conversion products was measured in a Packard liquid scintillation spectrometer with an efficiency for carbon-14 of 60% and an accuracy of ±5%. The total conversion of the substrate was calculated after chromatographic separation of the transformation products. Composition of conversion products was expressed in terms of per cent of radioactivity found in each identified steroid fraction.

Details of chromatography and identification of the steroid hormones will be published separately.[11]

RESULTS

1. *Excretion of Steroid Hormone Metabolites*

Preoperative levels of urinary 17-ketosteroids were in the range 8.5 to 60.7 mg./24 hr. (normal: 3-10 mg./24 hr.,), pregnanediol 7.1 to 23.5 mg./24 hr. (normal: 0.3-0.9 mg./24 hr., male; 0.7-5 mg./24 hr., female), and pregnanetriol 16.9 to 45.5 mg./24 hr. (normal: 0.7-2.5 mg./24 hr.), whereas no Porter-Silber chromogens or tetrahydrocortisone were detected during the studies. Fig. 4 shows that the

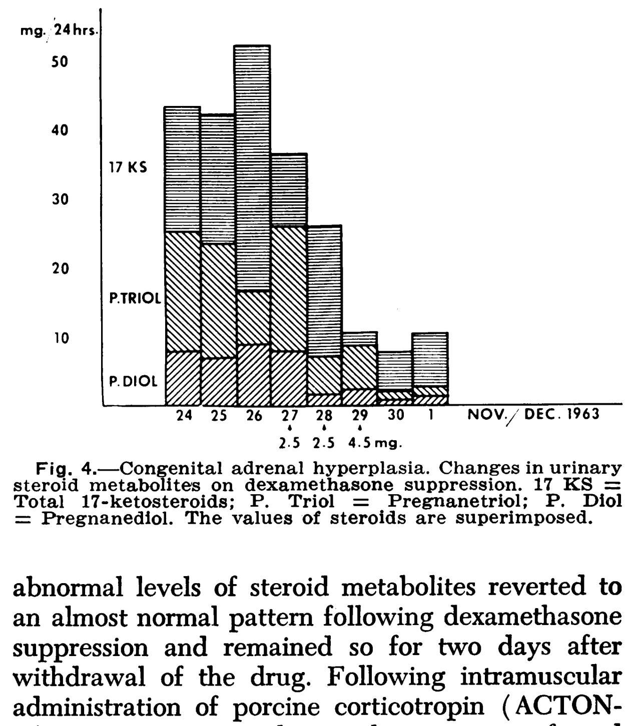

Fig. 4.—Congenital adrenal hyperplasia. Changes in urinary steroid metabolites on dexamethasone suppression. 17 KS = Total 17-ketosteroids; P. Triol = Pregnanetriol; P. Diol = Pregnanediol. The values of steroids are superimposed.

abnormal levels of steroid metabolites reverted to an almost normal pattern following dexamethasone suppression and remained so for two days after withdrawal of the drug. Following intramuscular administration of porcine corticotropin (ACTON-X) 20 I.U. every six hours, the excretion of total urinary 17-ketosteroids, pregnanediol and pregnanetriol increased markedly, but no Porter-Silber chromogens could be detected. Six months after panhysterectomy, the urinary excretion of steroid metabolites was re-evaluated (Fig. 5). On the day before the study (August 23), the cortisone maintenance dose was withdrawn and persistently high 17-ketosteroid, pregnanediol and pregnanetriol levels were found. After intramuscular administration of human chorionic gonadotropin (HCG*) 5000 I.U. for two days, a decrease in urinary pregnanediol and pregnanetriol was observed, whereas the total 17-ketosteroids increased. Following ACTH administration, pregnanediol and pregnanetriol excretions increased markedly, with no appreciable change in the levels of total 17-keto-

*"A.P.L.", chorionic gonadotropin (Ayerst).

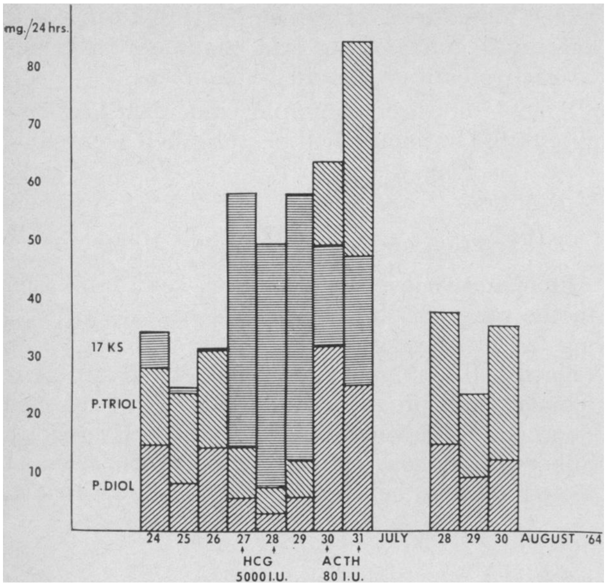

Fig. 5.—Congenital adrenal hyperplasia. Excretion of urinary steroids after panhysterectomy. 17 KS = Total 17-ketosteroids; P. Triol = Pregnanetriol; P. Diol = Pregnanediol. The values of steroids are superimposed.

steroids. The composition of C19 steroids shown in Table I indicates that at this time the main

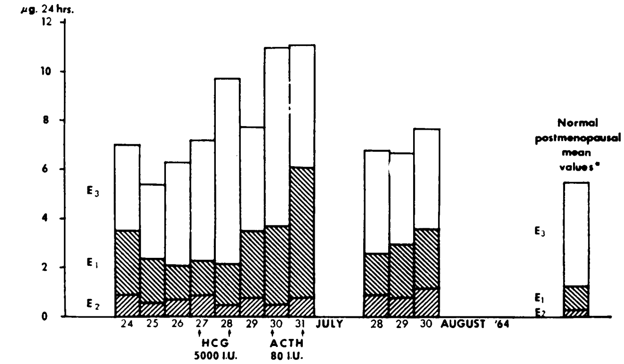

Fig. 6.—Congenital adrenal hyperplasia. Urinary estrogens after oophorectomy. Excretion of urinary estrogens after panhysterectomy. E_1 = Estrone; E_2 = Estradiol; E_3 = Estriol. The values of estrogens are additive.
*Normal postmenopausal mean values.[13]

menopausal woman[13] (Fig. 6). Administration of HCG and ACTH altered the excretion of urinary estrogens only to a minor degree. The presence of pregnanetriolone ($3\beta,17\alpha,20\alpha$-trihydroxypregnan-11-one) in the urine after β-glucuronidase hydrolysis was demonstrated using the method of Finkelstein[8] and, on semiquantitative estimation, the values were above 5 mg./24 hr. This metabolite of 21-deoxycortisol is practically undetectable in

TABLE I.—EXCRETION OF URINARY C19 NEUTRAL STEROIDS AFTER PANHYSTERECTOMY (MG./24 HR.)

Date	Medication	Andro.*	Etio.	DHEA	11-Keto-Etio.	11-OH-Andro.	Total
July 19, 1964							
24	None	9.1	3.6	4.1	—	—	16.8
25	None	4.9	2.3	1.8	0.2	1.1	10.3
26	None	7.3	3.8	1.2	—	—	12.3
27	HCG 5000 I.U.	3.6	3.2	2.3	—	—	9.1
28	HCG 5000 I.U.	8.4	4.1	1.7	Trace	Trace	14.2
29	None	7.4	5.1	5.0	—	—	17.5
30	ACTH 80 I.U.	8.3	4.3	4.5	—	—	17.1
31	ACTH 80 I.U.	5.5	4.3	3.5	Trace	Trace	13.3
Normal values		0.4 - 4.8	0.9 - 3.2	0.6 - 2.1	0.5 - 1.0	0.56 - 1.3	

*Andro. = Androsterone. DHEA = Dehydroisoandrosterone. 11-OH-Andro. = 11-hydroxyandrosterone.
Etio. = Etiocholanolone. 11-Keto-Etio. = 11-ketoetiocholanolone.

components of urinary 17-ketosteroids were androsterone, etiocholanolone and dehydroepiandrosterone with only occasionally detectable 11-ketoetiocholanolone and 11β-hydroxyandrosterone. Some increase on the second day after HCG was observed in the androsterone fraction. After discontinuation of HCG and administration of ACTH, the excretion of androsterone, etiocholanolone and dehydroepiandrosterone remained unchanged. The sum of individual 17-ketosteroids accounts for about one-half of the total 17-KS that were measured colorimetrically in terms of the dehydroepiandrosterone (DHEA) standard. This discrepancy is not unusual[12] and is attributed to the presence of other Zimmerman-positive components not measured by the gas-liquid chromatography.

The excretion of urinary estrogens, estrone, estradiol-17β and estriol after panhysterectomy was found to be in the range normally seen in the post-

normal subjects but appears in the urine of patients with congenital adrenal hyperplasia (CAH) who have a steroid 21-hydroxylase deficiency.[4-8]

The incompleteness of adrenal steroid 21-hydroxylase deficiency in this patient was revealed by assays of urinary aldosterone and corticosterone (Table II). In the absence of medication and with normal dietary sodium intake, the excretion of aldosterone was found to be within the normal limits, whereas corticosterone appeared in urine in amounts higher than in normal subjects. Excretion of aldosterone and corticosterone increased after ACTH administration.

2. *In vitro Metabolism of Steroids by Surviving Ovarian Tissue*

(a) *Progesterone as substrate.*—Biotransformation of progesterone-4-C^{14} by polycystic ovarian tissue from this patient has been compared with

TABLE II.—EXCRETION OF URINARY ALDOSTERONE AND CORTICOSTERONE

Date	*Medication*	*Aldosterone (μg./24 hr.)*	*Corticosterone (μg./24 hr.)*
July 25, 1964....	None	9.1	47.4
		7.8	53.6
		Average 8.45	Average 50.5
July 30, 1964...	ACTH 80 I.U.	14.7	83.2
		14.0	82.8
		Average 14.35	Average 83.0
		Recovery of standard 0.308 μg. 109%	Recovery of standard 0.449 μg. 111%

ovarian preparations from a patient with Stein-Leventhal syndrome and with several normally functioning ovaries. Under the experimental conditions used, the ovaries with polycystic structure converted two to four times more progesterone than did the normal ovaries (Table III). From

TABLE III.

Ovarian structure	*Normal*		*Polycystic*	
Diagnosis	Ca. breast	Congenital adrenal hyperplasia	Stein-Leventhal syndrome	
Age	34 - 43	16	21	
Ovarian tissue	0.8 - 1.5 g.	1.7 g.	1.5 g. (L. ovary)	1.1 g. (R. ovary)
Progesterone-4-C^{14}	6 - 15 μg.	15.4 μg.	9.2 μg.	9.2 μg.
Progesterone converted	20 - 40% (five ovaries)	79.4%	77.8%	56.3%
Composition of conversion products	%	%	%	%
	(range)			
17α-OH-progesterone	14 - 35	21.7	30.0	35.0
20α-OH-pregn-4-ene-3-one	24 - 49	15.3	7.9	13.4
20β-OH-pregn-4-ene-3-one	7 - 17	2.6	1.4	1.2
16α-OH-progesterone	4 - 13	13.6	11.1	14.1
6β-OH-progesterone	3 - 4	2.0	2.4	2.9
17α, 20α-O-H pregn-4-ene-3-one	2 - 4	2.5	2.6	3.1
Δ4-androstenedione	2 - 5	15.3	22.3	13.4
Testosterone	0.1 - 0.8	3.1	1.0	0.9
Estradiol-17β	0.01 - 0.1	0.01	0.1	0.1

progesterone, every ovarian preparation formed nine steroids which accounted for 70% to 80% of all the conversion products. The remaining conversion products have not been characterized. Normal ovarian tissue formed 17α-hydroxyprogesterone, 20α-hydroxy-pregn-4-ene-3-one, 20β-hydroxy-pregn-4-ene-3-one and 16α-hydroxyprogesterone as principal conversion products, whereas polycystic ovaries exhibited a different pattern in steroid hormone formation. Ovarian tissue from this patient formed considerably more △4-androstenedione than did the normal ovarian preparations. The biosynthesis of testosterone from progesterone precursor in normal ovaries was low and ranged from 0.1 to 0.8% of all the conversion products. Compared on a proportionate basis with other steroid hormones, the formation of testosterone by ovarian tissue from this patient was markedly increased. These *in vitro* observations indicate that the polycystic structure of the ovary in this case was associated with an increased potential for androgen formation. The *in vitro* formation of estradiol-17β from progesterone by the polycystic ovary from this patient was lower than that from ovaries of the patient with Stein-Leventhal syndrome.

(b) *Testosterone as substrate.* Incubation of testosterone-4-C^{14} with the surviving ovarian tissue from this patient yielded △4-androstenedione as the major conversion product and small amounts of 19-hydroxytestosterone, estradiol-17β and estrone. As shown in Table IV, estradiol-17β accounted for 0.2% and estrone for 0.1% of all testosterone conversion products. Unlike progesterone, the testosterone was metabolized by the ovarian tissue to a lesser extent. The aromatization of testosterone to estrogens by this tissue was about one-half that obtained with normal ovarian tissue under similar experimental conditions. Testosterone was also converted *in vitro* to several other products which have not been characterized.

TABLE IV.—CONVERSION OF TESTOSTERONE - 4 - C^{14} BY POLYCYSTIC OVARY

Tissue	*Testosterone - 4 - C^{14}*	*Testosterone converted*	*Recovery*
1.6 g.	68.6 μg. (5.16 μc.)	52.1%	95.5%

COMPOSITION OF CONVERSION PRODUCTS

△4-Androstenedione	68.5%
19-hydroxytestosterone	0.3%
Estradiol - 17β	0.2%
Estrone	0.1%
Unidentified	30.9%

(c) *Estrone as substrate.* Ovarian tissue *in vitro* transformed estrone-16-C^{14} mainly to estradiol-17β with the formation of small amounts of a non-ketonic material of higher polarity (Table V). The identity of the polar conversion product with estriol was disproved by crystallization. *In vitro* metabolism of estrone by this ovarian tissue was very similar to that seen with normal ovarian preparations.

TABLE V.—CONVERSION OF ESTRONE - 16 - C^{14} BY POLYCYSTIC OVARY

Tissue	*Estrone - 16 - C^{14}*	*Estrone converted*	*Recovery*
1.2 g.	28.6 μg. (1.3 μc.)	53.3%	95%

COMPOSITION OF CONVERSION PRODUCTS

Estradiol-17β	91.9%
Unidentified	9.1%

DISCUSSION

The problem of the pathogenesis of polycystic changes in the ovaries and associated abnormal endocrine function has received considerable attention in recent years. Clinical studies reviewed by Evans and Riley[14] and others[15, 16] indicate that polycystic ovaries are associated with conditions where the normal pituitary-ovarian relationship is distorted. That the increase in circulating androgens plays a role in the pathogenesis of follicular maturation arrest and polycystic changes in the ovaries is supported by the findings of such ovaries in patients with virilizing adrenal tumours, congenital adrenal hyperplasia and arrhenoblastoma.[2, 17, 18] Experimentally, prolonged treatment of young female rats with large doses of dehydroepiandrosterone and △4-androstenedione results in the formation of multiple ovarian follicular cysts.[19] Also, testosterone propionate given to young mice induces similar changes in the morphology of the ovaries.[20] It is believed that high levels of androgens modify the pituitary FSH/LH ratio, resulting in an inhibition of follicular maturation. Barraclough and Gorski[21] have presented evidence that the hypothalamus appears to be responsible for androgen-induced sterility. The circulating androgens apparently exert some conditioning effect on the hypothalamico-pituitary axis which results in an inappropriate gonadotropin secretion.[22] Apart from the hypothalamus, the androgens may also alter the ovarian responsiveness to gonadotropins. It has been observed in humans that the polycystic ovaries are highly sensitive to exogenous FSH and enlarge to a greater extent than do normal ovaries.[23] A high incidence of polycystic ovaries has been observed in closely inbred groups, suggesting a possibility of genetic factors which may be partly responsible for the development of this condition.[22]

The abnormal patterns of steroid hormone biosynthesis by polycystic ovaries have been noted by several authors.[24, 25] An increased formation of △4-androstenedione and also testosterone from progesterone as precursor has been frequently observed.[24, 25] Also a decreased capacity of estrogen formation has been described. In some cases the ovarian tissue exhibits deficiency in the conversion of △5-3β-ol structure to △4-3-keto configuration; as a result of this, the ovaries tend to produce increased amounts of dehydroepiandrosterone and △5-pregnenolone.[25] Recently, Axelrod, Goldzieher and Ross[26] presented evidence for the coexistence of 3β-ol-dehydrogenase deficiency in the ovary and in the adrenal glands.

In hirsute females with polycystic ovarian disease, an increased excretion of urinary pregnanetriolone has been described, whereas the 17-hydroxy and 17-keto steroids were found to be normal.[27] Pregnanetriolone, which is a metabolite of 21-deoxycortisol, is barely detectable in normal urine, but in patients with congenital adrenal hyperplasia it is excreted in milligram amounts, like those seen in the patient described in this communicaton. Apparently very minor abnormalities in the adrenocortical function may play an important role in the development of polycystic ovaries. A number of cases have been reported where normal ovarian function has been restored following a treatment with corticosteroids, not only in patients with the polycystic ovarian disease and apparently normal adrenocortical function but also in patients with congenital adrenal hyperplasia.[22]

It is believed that in the human ovary the steroid biosynthesis takes place in granulosa, theca and hilus cells.[28] The function and differentiation of these cells is dependent on the gonadotropin stimulation. This process may be modified by the hormonal environment and it appears to be partly influenced by the adrenocortical function.

The ovaries found in the present patient exhibited morphologically and biochemically similarities to the ovaries commonly found in young hirsute females with polycystic ovarian disease. Thus, in common with the Stein-Leventhal type, they exhibited considerably greater activity with respect to the *in vitro* metabolism of labelled progesterone than did the ovarian tissue from females with normal reproductive cycles. The most striking feature was the high conversion to the C19 steroids, testosterone and △4-androstenedione. These findings apparently reflect the hyperactive state of these ovaries and are in accord with the hypothesis of Leventhal,[18, 29] who suggested that polycystic ovarian disease is comparable with hyperactive states of other endocrine glands. It should be mentioned, however, that polycystic ovarian tissue from an adult with a virilizing adrenal tumour did not show an increased potential for progesterone metabolism to C19 steroids.[17] It is interesting to note that in the ovarian tissue from our patient the aromatization pathway which transforms androgens to estrogens was preserved, but was less efficient than in a normal reproductive ovary. These experimental findings suggest that the polycystic ovaries associated with congenital adrenal hyperplasia do not necessarily exhibit a complete absence of any of the enzymes in the steroid biosynthetic chain from progesterone to estrogens. There appears, however, to be an imbalance in steroid biosynthesis leading to an accumulation of androgens, and this may explain the development of secondary male characteristics of the patient at the time of puberty. It may be considered that the abnormal androgen-producing ovaries have functioned hormonally as testes.

In the metabolic studies performed in this patient after panhysterectomy it was noted that following administration of human chorionic gonadotropin the excretion of total urinary 17-ketosteroids increased. Perloff and Jacobsohn[30] have observed an extraovarian effect of human chorionic gonadotropin (HCG) on 17-ketosteroid metabolism in patients with Stein-Leventhal syndrome and suggested that the adrenal cortex in these patients is capable of responding to HCG. In normal humans the adrenal cortex apparently is not affected by HCG.[30] The significance of these observations at present remains obscure.

A recent report by Goldzieher[31] indicates that in patients with congenital adrenal hyperplasia the excretion of urinary estrogens is increased and remains so after gonadectomy. In this patient, after panhysterectomy, the three "classical" urinary estrogens—estrone, estradiol-17β and estriol—were found to be at the levels normally seen in postmenopausal women. Administration of HCG and ACTH resulted in only slight changes in these levels.

Several features of the adrenocortical function and steroid metabolism in our patient cannot be explained by a simple assumption of steroid 21-hydroxylase deficiency. In spite of a complete lack of cortisol secretion as suggested by an absence of urinary Porter-Silber chromogens and tetrahydrocortisone, there were no detectable signs or symptoms of adrenal cortical insufficiency, even after withdrawal of cortisone therapy. This suggests that the adrenal glands were secreting corticosteroids which were compensating for the deficiency of cortisol. Determination of urinary nonmetabolized corticosterone has revealed that this glucocorticoid was excreted in higher amounts than usually seen in normal persons. It is likely that corticosterone played an important role in compensating for the lack of cortisol. Urinary aldosterone was normal, which finding may account for the well-maintained electrolyte balance in this individual. Both corticosterone and aldosterone are 21-hydroxylated steroids and their production, in the face of all the evidence for a deficiency in steroid 21-hydroxylase activity, may be explained on the grounds of adrenocortical functional zonation. It has been experimentally shown that aldosterone and corticosterone are synthesized in the zona glomerulosa of the adrenal cortex.[32] Symington and Jeffries[33] have pointed out that in several patients with congenital adrenal hyperplasia this particular adrenal zone is two to four times wider than in normal adrenals. Apparently in this patient the zona glomerulosa has compensated for the deficiency of biologically active steroid secretion from the innermost adrenal zones (fasciculata and reticularis). This suggests that the genetically determined abnormalities of steroid biosynthesis appear to be limited to the fasciculata and reticularis zones. It has also been demonstrated that the formation of aldosterone and corticosterone in this subject is influenced by exogenous ACTH.

SUMMARY

Ovaries with structure similar to that seen in polycystic ovarian disease have been found in a 16-year-old female who also had congenital absence of vagina, the presence of male-like external genitalia and congenital adrenal hyperplasia. Masculinization of this individual was sufficiently severe to cause the patient to be reared as a male. Biochemical studies on ovarian tissue from this individual revealed a hyperactivity and an imbalance of enzyme systems concerned with the steroid-hormone biosynthesis, which led to a production of large amounts of androgens (testosterone and Δ4-androstenedione). The pathway towards estrogens was preserved but less efficient than in normal ovarian tissue.

Studies of urinary steroid metabolites before and after hysterectomy and bilateral salpingo-oophorectomy revealed an absence of Porter-Silber chromogens and tetrahydrocortisone. Excretion of aldosterone was normal and that of corticosterone slightly higher than normal. The patterns of urinary 17-ketosteroids, pregnanediol, pregnanetriol and pregnanetriolone were similar to those commonly seen in congenital adrenal hyperplasia with steroid 21-hydroxylase deficiency.

Urinary estrogens after panhysterectomy were low, being in the range of postmenopausal women. The pathogenesis of polycystic ovaries and their possible contribution to masculinization are discussed.

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